REMARKS

Claims 1, 3-18, and 21-25 are pending. Claims 2, 19, and 20 are canceled. Applicants reserve the right to pursue any canceled subject matter in one or more continuation, divisional, or continuation-in-part applications.

Support for Amendments

Claim 1 is amended to incorporate original claim 2. Claims 3 and 17 are amended according to US practice for dependencies. Support can be found in the specification as filed, including the original claims. New claims 22-25 are added as various embodiments of the invention. Support can be found in the specification as filed, for example at page 9, lines 11-13, or at page 7, lines 13-16.

No new matter is entered.

Objections to Claims

Claims 17-20 are objected to as being in improper form with regard to multiple dependencies. By amendment, claims 19-20 are canceled, and claims 17-18 are amended according to US practice for dependency. Applicants request withdrawal of the objection and examination on the merits for the pending claims.

Rejection Under 35 U.S.C. § 102(b)

Claims 1 is rejected under 35 U.S.C. § 102(b) as being anticipated by Bowman et al. (WO 00/69441, published November 23, 2000). Applicants respectfully traverse. By amendment claim 2 is canceled, and claim 1 is amended to incorporate claim 2. Bowman does

not disclose the treatment of cancer by using the combination of ET-743 with a 5-fluorouracil prodrug. Applicants respectfully request withdrawal of the rejection.

Rejection Under 35 U.S.C. § 103

Claims 1-16 and 21 are rejected under 35 U.S.C. § 103 as being unpatentable over Bowman et al. (WO 00/69441, published November 23, 2000) in view of Ishikawa et al. (Biochemical Pharmacology, 1998, vol. 55, pages 1091-1097). The Office Action argues that it would have been obvious to use capecitabine in combination with ET-743 according to the teachings of Bowman in view of Ishikawa, and that "[s]election of appropriate dosage regimens will vary according to the particular formulation, mode of applicant, and the particular *situs*, host and tumor being treated, and such selection would have been well within the purview of the skilled artisan" (Office Action, page 5, lines 5-8). Applicants respectfully traverse the rejection.

U.S. case law holds that a proper obviousness inquiry requires four factual inquiries: (a) determining the scope and contents of the prior art; (b) ascertaining the differences between the prior art and the claims in issue; (c) resolving the level of ordinary skill in the pertinent art; and (d) evaluating evidence of secondary consideration. See *Graham v. John Deere*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). Although the Supreme Court in KSR recently rejected a rigid application of the "teaching, suggestion, motivation" test, the Court did recognize that a showing of "teaching, suggestion, or motivation " to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a). See *KSR Int'l Co. v. Teleflex, Inc.*, No 04-1350 at 15 (U.S. Apr. 30, 2007). The Court further noted that an analysis supporting a rejection under 35 U.S.C. § 103(a) should be made explicit, and that "it can be important to

identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR*, slip op. at 14.

Therefore, Applicants respectfully traverse the rejection on the basis that 1) the references fail to teach all of the claimed elements, and 2) the references fail to provide a reason for one of ordinary skill in the art to arrive at the claimed elements. These factors provide a helpful insight in determining obviousness, and in view of these factors, the claims are not obvious under 35 U.S.C. § 103(a) from the combination of cited references.

Applicants note that the prior art actually teaches away from the combination of ET-743 with 5-fluorouracil. For example, see Takahashi et al. ("Sequence-dependent Synergistic Cytotoxicity of Ecteinascidin-743 and Paclitaxel in Human Breast Cancer Cell Lines in Vitro and in Vivo," Cancer Research, vol. 62, pages 6909-6915, December 1, 2002, considered by the Examiner in the IDS submitted May 11, 2006 and signed by the Examiner on October 28, 2007). According to Takahashi (page 6914, 2nd column, 2nd paragraph), "[a]nother drug used to treat breast cancer, 5-FU, appears not to be a good partner of ET-743. Moderate antagonism was observed for the combination of ET-743 and 5-FU when ET-743 was administered concomitantly. This antagonistic cytotoxicity was not improved by altering the sequence schedule." By teaching away from the combination of ET-743 and 5-fluorouracil, Takahashi is also teaching away from the combination of ET-743 with a 5-fluorouracil prodrug.

With regard to the actual results in the specification, the instant application shows that the combination of ET-743 and capecitabine resulted in clinical improvement in human patients, and that seven patients (4 sarcoma patients, 1 each of gastric, breast, vaginal, and adenocarcinoma patients) had stable disease and 1 patient with cholangiocarcinoma had a partial response (see Specification, page 13, last paragraph). Neither Bowman nor Ishikawa provide a

teaching for the dose ranges for the combination of ET-743 and capecitabine which result in clinical improvement in human cancer patients, for example 0.75-1.4 mg/m^2 of ET-743 and 1500-2500 mg/m^2/day as claimed. Applicants note a report cited on the accompanying Information Disclosure Statement (Gore *et al.*, "Phase I Combination Study of Trabectedin and Capecitabine in Patients with Advanced Malignancies," Poster Presentation, 42nd ASCO Annual Meeting held on June 2-6, 2006, Atlanta, Georgia) finds a recommended dose for humans of 1600 mg/m^2/day for capecitabine administered during 14 days and 1.1 mg/m^2 for ET-743 administered once every three weeks.

Therefore, the combination of Bowman and Ishikawa fails to teach all of the claimed elements, and the references fail to provide a reason for one of ordinary skill in the art to arrive at the claimed elements. Applicants respectfully request withdrawal of the rejection.

CONCLUSION

Based on the foregoing amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **50-3732**, Order No. 13566.105023. In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **50-3732**, Order No. 13566.105023.

Respectfully submitted,
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